Dry powder inhaler formulations- effect of polymer carrier size on the drug dispersion

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Summary

Background: The size of the carrier influences drug aerosolization from a dry powder inhaler (DPI) formulation. Lactose particles with irregular shape and rough surface in a variety of sizes are traditionally used as carriers; however, contradictory reports exist regarding the effect of carrier size on the dispersion of drug. We examined the influence of the spherical particle size of the biodegradable polylactide-co-glycolide (PLGA) carrier on the aerosolization of a model drug, salbutamol sulphate (SS).
Methods: Four different sizes (20-150 µm) of polymer carriers were fabricated using solvent evaporation technique and the dispersion of SS from these carriers was measured by a Twin Stage Impinger (TSI). The size and morphological properties of polymer carriers were determined by laser diffraction and SEM, respectively.
Results: The fine particle fraction (FPF) was found to increase significantly (ANOVA, $p<0.0001$) from 5.6% to 21.3% with increasing carrier size from 20 µm up to150 µm.
Conclusions: The aerosolization of drug increased linearly with the size of polymer carriers. For a fixed mass of drug particles in a formulation, the mass of drug particles per unit area of carriers is higher in formulations containing the larger carriers, which leads to an increase in the dispersion of drug due to the increased mechanical forces occurred between the carriers and the device walls.

Introduction

Dry powder inhaler (DPI) formulations are one of the most useful aerosol preparations in which drugs are formulated as interactive mixtures with micronised drug particles (<5 µm), adhered onto the surface of large inert carriers, which enhance the flow property of the formulation for better aerosolization. The size of the carrier influences the aerosolization performance of drug from a drug–carrier mixture. Currently, different grades of lactose-based dry powder inhaler (DPI) formulations are available and contradictory reports exist regarding the size effect of the carrier on the aerosolization of drugs. Some studies demonstrated an increase drug dispersion with increasing carrier size(1, 2) while other studies suggested the reverse(3-5). For example, using binary mixtures of salbutamol sulfate and synthesized sugar, the fine particle fraction (FPF) decreased with increasing carrier particle size(5). A reduction in carrier size improved FPF of albuterol sulfate and budesonide(6). However, a higher respirable fraction of terbutaline sulfate was obtained from coarser lactose (53–105 µm) than from a finer lactose (<53 µm)(1). Other factors such as carrier surface roughness, shape and the presence of fine excipients in the formulations also contribute to the efficient dispersion of drug from DPI formulations. Lactose particles are irregular in shape with wider size distribution which may have contributed to the contradictory reports. Using different sizes of polystyrene spheres as the carriers, Ooi et al. have demonstrated the decreased aerosol performance of salbutamol sulphate (SS) with increased carrier size(7). Recently, Tuli et al reported the applicability of biodegradable polycaprolactone (PCL) microparticles as carriers for SS dispersion and increased dispersion of drug was observed with increased carrier sizes(8). These contradictory results suggested an effect of the polymer structure on DPI performance and convinced us to extend the effect of size on drug dispersion using another biodegradable polymer, polylactide-co-glycolide (PLGA). Therefore, the aim of the present study was to examine the influence of the intrinsic particle size of the polylactide-co-glycolide (PLGA) microcarrier on the aerosolization of drug from the DPI formulation. The biodegradable PLGA represents different surface functionalities in relation to PCL or polystyrene microcarriers. To get a better understanding of the polymer carrier size, PLGA microspheres of four different approximate sizes (20 µm, 45 µm, 90 µm and 150 µm) were fabricated and the relationship between carrier size and SS dispersion was investigated.

Experimental

Chemicals: Inhalation grade Salbutamol Sulfate (SS) was obtained from GlaxoSmithKline, Australia. Poly (DL-lactide-co-glycolide) 50:50 was purchased from SurModics Pharmaceuticals, USA and polyvinyl alcohol (87-89% hydrolyzed, was obtained from Sigma Aldrich. Tween 80 and ammonium acetate were purchased from Ajax Chemicals, Australia. HPLC grade methanol (LiChrosolv®) was purchased from Merck, Germany.
Preparation of PLGA microspheres: Using solvent evaporation technique, the PLGA microparticles of various sizes (20-150 µm) were prepared. The polymer PLGA was dissolved in dichloromethane (DCM) at 10%, 15% and 20% concentration. This polymer solution was added dropwise into 1% w/v aqueous Polyvinyl Alcohol (PVA) solution. The emulsion was stirred at 2000- 6000 rpm with an overhead stirrer (IKA® Eurostar power-control-visc-6000, Labtek) for 60 minutes under ambient pressure. Finally the microspheres were collected by filtration, washed with deionized water and dried in a vacuum desiccator at room temperature.
Measurement of particle size: Using laser diffraction (Malvern Mastersizer, Malvern Instruments Ltd, UK) the size and size distribution of PLGA microparticles was determined. The PLGA carrier particles (400 mg) were

dispersed in 5 mL of water containing Tween-80 with the aid of sonication in a water bath for 5 minutes. This sonicated sample was added dropwise to the sample cell containing 100 mL of distilled water until an obscuration between 15-30% was obtained to optimize sensitivity. The average particle size and size distributions were measured from five replicate of each sample.

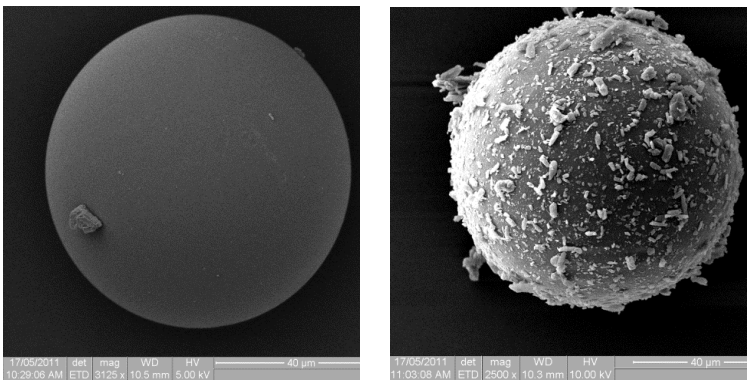
DPI formulation and dispersion: The mixing of PLGA microspheres with SS (2.5%) was performed by a validated hand mixing method. The drug powder was placed between two layers of PLGA powder in a glass test tube along with three ceramic beads of approximately 10 mm in diameter. The test tube was vigorously shaken by hand for 5 minutes to ensure proper mixing. During this process, ceramic beads provided a ball milling effect for breaking up the agglomerates formed during mixing. The powder formulations were loaded (20 mg) into hard gelatine capsules (size 3, Fawns and McAllan Pty Ltd., Australia) and the dispersion of SS from interactive mixtures was determined by a Twin Stage Impinger (TSI) with a Rotahaler® at an airflow rate of 60 L/min. The aerodynamic cut-off diameter at 60L/min was 6.4µm. The active drug was quantified by a validated HPLC method.

Results and discussions

PLGA microspheres were fabricated in four different sizes: 20 µm, 45 µm, 90 µm and 150 µm by varying the concentration of the polymer and the speed of the stirring (Table 1). The SEM images showed very smooth surface and no pores observed in PLGA carriers (Figure 1). Interactive mixtures of these carriers and SS (2.5% w/w) were prepared and the reproducible content uniformity of SS was obtained for all formulations. The accuracy ranged from 99.4%- 99.9% and the coefficient of variance (CV) was below 2.0% (Table 2). The FPF of SS (n = 5) from the different sizes of PLGA carriers was found to increase significantly (ANOVA, $p<0.0001$) from 5.6% to 21.3% as the carrier size increased. A linear relationship ($R^2 = 0.9574$) between the FPF of SS from PLGA microspheres and the size of the microspheres is presented in Figure 2, where an increased deposition of the SS particles from the surfaces of PLGA carriers was observed with increasing carrier size. The actual mechanism by which SS particles detached from smaller or larger carriers and their subsequent influence in the performance of drug dispersion from the polymer carrier based DPI formulation is unclear. As demonstrated in our previously published article(8), for a given formulation mass with a fixed formulation ratio, the mass of SS particles per carrier is increased on the larger carrier surface due to the reduction in the carrier particle number. As the drug-carrier ratio for each size of the carrier microspheres was constant (i.e., 2.5% w/w SS), the surface payload was not different from carrier to carrier. Thus for a fixed mass of drug, the mass of SS particles per unit area of carrier particles is more in larger carriers as compared with the smaller microspheres due to the reduction in the carrier particle number in the formulation. Therefore, due to the increased carrier size, the specific surface area of PLGA microspheres, calculated from the volume median diameter (VMD) of particles determined by laser diffraction, was decreased and there was an increase in the number of drug particles per carrier.

Table 1: Parameters for preparing different sizes of PLGA microspheres

Average VMD of microspheres(µm)	Concentration of polymer (% w/v)	Speed of stirring (rpm)
20	10	6000
45	10	2000
90	15	2000
150	20	2000



A B

Figure 1. The SEM images of PLGA microparticles: A. PLGA particle, B. Interactive mixture of PLGA and 2.5%w/w SS, where SS particles are adhered to the surface of carrier particles.

Table 2: Content uniformity of formulations of 2.5% SS- PLGA microparticles (n = 20)

Formulations	Accuracy (%)	% CV
Size 20 µm	99.9	0.9
Size 45 µm	99.8	0.5
Size 90 µm	99.4	1.1
Size 150 µm	99.6	0.7

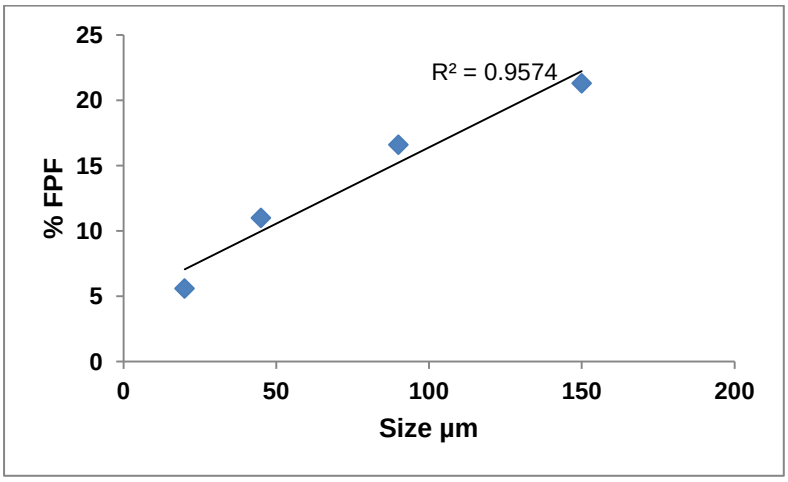


Figure 2. The relationship between the FPF of SS and the size of the PLGA microspheres, n=5

Detachment of drug particles from the carriers by mechanical forces occurs when collisions occur between the carrier particles and the inhaler wall and between the carrier particles. Due to the collisions, there is a transfer of momentum that depends on the mass and the velocity of the carriers. The force of mechanical detachment is directly proportional to the cube of carrier particle diameter (Force = Mass x Acceleration, where, Mass = Density x Volume, and Volume = $4/3\pi r^3$). From this equation, it can be explained that the larger particles with greater mass produced high impaction which in turn generated greater detachment forces, which eventually caused an increase in the FPF of the drug. Therefore the larger carriers showed increased mechanical detachment forces due to the stronger particle-inhaler and particle-particle collisions (9). Collisions with the device or with other particles result in sudden acceleration of the large particles or agglomerates and these can be large enough to result in better drug dispersion.

Smaller carriers had increased specific surface area with subsequent increase in the overall surface energy, expected to be the cause of higher adhesive forces between drug and the PLGA carriers. In addition, cohesive and frictional resistance increases due to more points of contact arising from the increase in surface area-to-volume ratio for smaller carriers (10) and thereby reduced aerosolization behaviour was observed. Furthermore, it has been suggested that the smaller size particles are more susceptible to the influence of van der Waals forces (11), which might affect the SS dispersion from smaller carriers. Thus, all of these factors might have contributed to the decreased detachment of the SS from the smaller carriers compared to that of larger carrier. Therefore, as the mechanical forces increased with the larger carrier particles, the role of the increased size of the carrier particles was confirmed in improving the dispersion performance of the drug.

We have used only four different sizes of PLGA carriers and the maximum particle size employed in the present study was 150 µm. The effect of carriers larger than 150 µm could have produced different pattern of drug dispersion from the formulations. It is speculated that with further increasing the carrier size it may encounter reduced velocity due to its increasing mass which can affect the drug dispersion. Therefore, further studies are warranted to establish the optimum carrier size for efficient drug dispersion.

Conclusion

This study concluded that the size of biodegradable PLGA microparticles played a significant (ANOVA, $p<0.0001$) role in enhancing the aerosolization of SS from a DPI formulation. As the carrier size increased, there was an increased mechanical force experienced by larger carriers which resulted in easy detachment of the drug particles from the surfaces and eventually increased FPF of SS. This outcome suggested that the larger size of the PLGA carriers was effective in improving the dispersion of the drug from the carrier surfaces.

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